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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,974	11/19/2001	Jennifer L. Hillman	PF-0183-2 DIV	4346

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,974	HILLMAN ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-81* is/are pending in the application.

4a) Of the above claim(s) *62,68,69 and 72-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-67,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/19/01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Alignment (2 pages)*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group II in Paper No. 11062003 is acknowledged. The traversal is on the ground(s) that the search for inventions I and II would not constitute an unduly burdensome search. This is not found persuasive because the inventions of group I and II are classified in different class and subclasses and are made and used different processes for different purposes. Furthermore, the search for the nucleic acid of the elected group is not coextensive to the search for the protein of group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-61 are canceled without prejudice of disclaimer, claims 62-81 are newly added. Claims 62, 68-69, and 72-81 are withdrawn from further consideration as being drawn to non-elected inventions.

3. Claims 63-67 and 70-71 are examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statement filed 11/19/2001 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 63-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 63 and dependent claims thereof, it is vague and indefinite because it depends from non-elected claim 62. For examination purposes, the limitations of non-elected claim 62 will be read into the examined claims. Applicants may obviate this rejection by rewriting the claim in independent form.

Claim Rejections - 35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 63-67 and 70-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set for the nucleic acid sequence that encodes the protein of SEQ ID No: 5 and comprises the nucleic acid sequence of SEQ ID No: 6, and therefore not commensurate in scope to claims that read of nucleic acid sequences that are 90% identical to SEQ ID No: 6 or encode proteins that are 90%identical to SEQ ID No: 5. Furthermore, the written description is also not commensurate in scope to claims that read on nucleic acid sequences encoding biologically active fragments or immunogenic fragments of SEQ ID No: 5, polynucleotides that are complimentary to sequences that are 90%identical to SEQ ID No: 6, or any RNA equivalents thereof of SEQ ID No: 6 (i.e.

90%identical to SEQ ID No: 6, compliment of SEQ ID No: 6 or compliment of a 90% identical sequence of SEQ ID No: 6).

The claims recite nucleic acid sequences that encode proteins that are 90% identical to SEQ ID No: 5, biological and immunogenic fragments of SEQ ID No: 5, nucleic acid sequences that are at least 90% identical to SEQ ID No: 6, complementary sequences to SEQ ID No: 6, and any RNA equivalents of SEQ ID No: 6 (i.e. 90%identical to SEQ ID No: 6, compliment of SEQ ID No: 6 or compliment of a 90% identical sequence of SEQ ID No: 6). However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides for sequence that are 90% homologous, fragments (either biologically active or immunogeneic), or equivalents of either SEQ ID No: 5 or 6. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice all sequences that are 90%identical, fragments (either biologically active or immunogeneic), or RNA equivalents of either SEQ ID No: 5 or 6. Neither has Applicant provided a sufficient written description of any structure that may be correlated with any specific function, so as to provide the skilled artisan with a means of screening such embodied claim limitations. A sequence that is 90% identical to either SEQ ID No: 5 or 6 encompasses *any* molecule from any species of animal provided that it is 90%identical to SEQ ID No: 5 or 6, of which only sequences from human have been taught. This is not disclosure is not sufficient enough to be entitled to the broad genus of any sequence which is 90%identical. Furthermore, the fragments or RNA equivalents claimed, have not been ascribed a specific structure (i.e. a specific nucleic acid sequence or amino acid sequence), so as to allow one skilled in the art to identify whether all fragments of either SEQ ID No: 5 or 6 were in the possession of the inventor at the time the invention was made. Thus the genus of sequences encompassed by the claims is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Support for homologous sequences, fragments, or RNA equivalents is provided in the specification on page 13 lines 26-30 and page 19, lines 5-8 for example, however, no disclosure, beyond the mere mention of homologous sequence, fragments or RNA equivalents are made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore only a nucleic acid of SEQ ID No: 6 encoding the protein of SEQ ID No: 5 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 63-67 and 70-71 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantially asserted utility or a well established utility.

The disclosed utilities for the HRABS-3 nucleic acid comprising SEQ ID No: 6 and encoding SEQ ID No: 5, homologous sequence, fragments (biologically active and immunogeneic), and RNA equivalents of SEQ ID No: 6 include the diagnosis, prevention, treatment of immune system disorders, cancer, and diseases involving vesicle targeting, membrane fusion, or fusion, or protein processing, targeting or secretion. However, neither the specification nor any art of record teaches what the HRABS-3 nucleic acid is, how it functions, or a specific and well-established utility for any of the fragments claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease.

The specification further proposes, based on sequence similarity to rat Rab28, rabbit Rab25, and canine Rab9, that the HRABS-3 will have similar biological effects and activities (page 3, line 6-8, for example). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in

any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and

characteristics of a protein. Thus, despite the 99% homology between canine Rab9 and HRAB-3, there is still a 1% difference and it cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein. Further even if the polypeptide of SEQ ID NO: 5 encoded by the nucleic acid of SEQ ID No: 6_is structurally similar to rat Rab28, rabbit Rab25, and canine Rab9, neither the specification nor any art of record teaches what the polypeptide is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active as claimed in a pharmaceutical composition.

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of

respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a dissimilarity, to rat Rab28, rabbit Rab25, and canine Rab9, the function of the SEQ ID NO:5 polypeptide encoded by the nucleic acid of SEQ ID No: 6 could not be predicted, based on sequence similarity with rat Rab28, rabbit Rab25, and canine Rab9, nor would it be expected to be the same as that of rat Rab28, rabbit Rab25, or canine Rab9.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims63-67 and 70-71 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 63, 66,67, and 70-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Lombardi D *et al* (EMBO J. 1993, 12(2):677-82, applicant **IDS 22**). Lombardi *et al* disclose a nucleic acid sequence that encodes a polypeptide sequence that is at least 90% identical to SEQ ID No: 5, wherein the nucleic acid which encodes said polypeptide is operably linked to a promoter, and a cell that has been transformed with said nucleic acid sequence. It is further disclosed by Lombardi *et al* that the nucleic acid sequence is at least 90% identical to that of SEQ ID No: 6 and has at least 60 contiguous nucleotide sequences of SEQ ID No: 6.

12. Claims 63, 64, 65, 66, 70 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Ioannou YA *et al* (Entrez Accession number G02361, submitted December 1995). Ioannou YA *et al* publicly disclosed a sequence which is identical to SEQ ID No: 5, which is encoded by SEQ ID No: 6. It is noted that if the applicant is able

to overcome this rejection by antedating the reference, a 102(a) rejection would still apply. Although the reference does not specifically teach that the nucleic acid sequence is operably linked to a promoter sequence, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful; the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
February 20, 2004

GARY NICKOL
PRIMARY EXAMINER